Filgrastim DP

Pharmacology

Hematopoietic growth factor. Interacts with receptors on the surface of hematopoietic cells and stimulates cell proliferation, differentiation and functional activation. Human granulocyte colony-stimulating factor (G-CSF) is produced by monocytes, fibroblasts and endothelial cells. G-CSF regulates neutrophil production and the release of functionally active neutrophils from the bone marrow into the blood. G-CSF is not specific for neutrophils only, in vivo and in vitro studies have shown minimal direct effect on the production of other hematopoietic cells. In Phase I clinical trials with the inclusion of 96 patients with various nonmyeloid malignancies, filgrastim when administered by different routes - v/v (1-70 µg/kg 2 times a day) p/k (1-3 µg/kg once daily) or by prolonged p/k infusion (3-11 µg/kg/day) has been shown to dose-dependently increase the number of circulating neutrophils with normal functional activity in blood (shown by chemotaxis and phagocytosis studies). After treatment with filgrastim the number of leukocytes returned to the initial level in most cases within 4 days. An increase in lymphocyte count against the background of filgrastim was recorded in healthy patients and in patients with cancer. In clinical trials, it was noted that in differential leukocyte counts there was a shift of the formula to the left with the appearance of granulocytic precursor cells, including promyelocytes and myeloblasts. In addition, the appearance of Dohle bodies, increased granulocyte granulation, and hypersegmentation of neutrophils were noted. These changes were transient.

Indications

Neutropenia (including in patients receiving cytostatic drugs for nonmyeloid malignancies); reduction of duration of neutropenia and its clinical consequences in patients preparing for bone marrow transplantation; persistent neutropenia in patients with advanced stage of HIV infection (absolute neutrophil count 1000 cells/µl or less); mobilization of peripheral stem cells (including after myelosuppressive therapy). including after myelosuppressive therapy); neutropenia (hereditary, recurrent or idiopathic - neutrophil count is less or equal to 500 cells/µL) and severe or recurrent infections (history) within last 12 months.

Contents and product form

Solution for intravenous and subcutaneous administration	1 fl.
filgrastim	30 million units (300 micrograms)
	48 million units (480 micrograms)
Additional ingredients: sorbitol, polysorbate 80, glacial acetic acid, sodium hydroxide, water for injection	

1 ml (30 ml IU) or 1.6 ml (48 ml IU) in a vial; 5 vials in a carton box.

Chemical name

N-L-Methionyl-colony-stimulating factor (human genetically engineered); non-glycosylated protein composed of 175 amino acids

Characteristics

Stimulant of leukopoiesis. It is produced by laboratory strain of Escherichia coli bacteria, into which a gene of human granulocytic colony-stimulating factor was introduced by genetic engineering methods.

Sterile, colorless liquid for parenteral administration. Molecular weight is 18800 Da.

Contraindications

Hypersensitivity, severe congenital neutropenia with abnormal cytogenetics (Kostmann syndrome), increased doses of cytotoxic chemotherapeutic agents above recommended, hepatic and/or renal insufficiency, age less than 1 year.

Limitations to use

Malignant and pre-tumor diseases of myeloid nature, combination with high-dose therapy.

Application during pregnancy and lactation

During pregnancy it is possible if the expected effect of the therapy exceeds the potential risk for the fetus (no adequate and strictly controlled trials have been conducted, the safety for pregnant women has not been established).

Studies in rabbits have shown that filgrastim causes side effects in pregnant rabbits when administered in doses 2-10 times higher than in humans. When filgrastim was administered to rabbits at doses of 80 µg/kg/day, an increased incidence of miscarriage and embryo failure was observed. Filgrastim administered to pregnant rabbits at doses of 80 µg/kg/day during organogenesis resulted in urogenital bleeding, decreased food intake, increased fetal resorption, developmental abnormalities, decreased body weight, and fewer viable calves. No external abnormalities were observed in fetuses of females receiving doses of 80 µg/kg/day.

Studies in pregnant rats with daily IV injections during organogenesis at dose levels up to 575 µg/kg/day showed no evidence of lethality, teratogenicity, or behavioral effects in the offspring.

It is not recommended for use in breastfeeding mothers (it is unknown whether filgrastim penetrates into breast milk).

Side effects of the substance Filgrastim

Cancer patients receiving myelosuppressive chemotherapy

In clinical trials involving more than 350 patients who received filgrastim after cytotoxic chemotherapy, most side effects were a complication of the underlying malignant disease or cytotoxic therapy. In the Phase II and III studies, filgrastim treatment was accompanied by bone pain in 24% of patients. As a rule, these pains were mild to moderate and in most cases were treated with the usual analgesics; rarely bone pain was severe and required narcotic analgesics. Bone pain was more frequent in patients receiving filgrastim w/v in high doses (20-100 mcg/kg/day) and less frequent in patients receiving filgrastim p/k in low doses (3-10 mcg/kg/day).

In randomized, double-blind, placebo-controlled trials, adverse reactions were noted with filgrastim therapy (4-8 mcg/kg/day) after combination chemotherapy in patients (N=207) with small-cell lung cancer (see table). The adverse effects noted in patients who received filgrastim/chemotherapy and placebo/chemotherapy are presented.

Adverse effects reported in clinical trials

No serious, life-threatening, or fatal reactions associated with filgrastim therapy were reported in the study.

Spontaneous reversible mild to moderate increases in uric acid, LDH, and ALP levels in 27-58% of 98 patients who received filgrastim after cytotoxic therapy. In Phase III clinical trials, 7 of 176 patients reported a transient decrease in BP (<90/60 mm Hg) after filgrastim administration that did not require additional treatment. Cardiac effects (myocardial infarction, arrhythmias) were reported in 11 of 375 cancer patients who received filgrastim in clinical trials; their causal relationship with filgrastim therapy has not been established.

Cancer patients with bone marrow transplantation

In clinical trials in patients receiving intensive chemotherapy after bone marrow transplantation, the most common side effects in both the control and the main group were stomatitis, nausea and vomiting, mostly mild to moderate in severity; no association with filgrastim administration was established. In a randomized study involving 167 patients, patients who received filgrastim more frequently than the control group had the following effects (percentages in parentheses are shown for patients and placebo group): nausea (10/4), vomiting (7/3), hypertension (4/0), rash (12/10), peritonitis (2/0). The causal association of these effects with filgrastim therapy has not been established. One case of erythema nodosum of moderate severity and possibly related to filgrastim therapy has been reported.

In general, the side effects observed in the non-randomized trials were similar to those observed in the randomized trials and were mild to moderate in severity. One study (N=45) reported 3 cases of serious adverse events related to filgrastim therapy - renal failure (2), increased capillary permeability syndrome (1). The relationship of these cases with filgrastim remains unclear, since they were recorded in patients with proven infection with clinical manifestations of sepsis, who received potentially nephrotoxic antibacterial and/or antifungal drugs

Patients with severe chronic neutropenia (TCN)

In clinical trials, approximately 33% of patients had mild to moderate bone pain. In most cases, these pains were managed with conventional analgesics. In addition, generalized musculoskeletal pain was more common with filgrastim compared to placebo. An enlargement of the spleen was noted in approximately 30% of patients. However, abdominal pain or flank pain and thrombocytopenia (<50000 cells/mm3 in 12% of patients) were infrequent in patients with a palpable spleen. Less than 3% of patients (most had splenomegaly) underwent splenectomy. Less than 6% of patients had thrombocytopenia (<50000 cells/mm3) during filgrastim therapy, most of whom had prior thrombocytopenia. In most cases, thrombocytopenia subsided with dose reduction or discontinuation of therapy. In addition, 5% of patients had platelet counts of 50000-100000/mm3. No serious hemorrhagic complications associated with filgrastim administration were observed in these patients. Nasal bleeding was observed in 15% of patients treated with filgrastim, but was associated with thrombocytopenia in 2% of patients. Anemia was noted in about 10% of patients, but in most cases was associated with frequent diagnostic phlebotomy, chronic disease, or concomitant drug treatment. In clinical trials, approximately 3% of patients (9/325) developed myelodysplasia or leukemia while taking filgrastim. In 12 of 102 patients with normal cytogenetic evaluations at baseline, abnormalities, including monosomy 7, were found at follow-up evaluations after 18-52 months of filgrastim therapy. It is unknown whether the development of these phenomena is a consequence of continuous daily administration of filgrastim or reflects the natural development of TCH. Side effects possibly associated with filgrastim treatment and reported in less than 2% of patients with TCHN included: injection site reactions, headache, liver enlargement, joint pain, osteoporosis, cutaneous vasculitis, hematuria and proteinuria, hair loss, skin rash, exacerbation of some pre-existing skin conditions (e.g., psoriasis).

Interactions

The safety and efficacy of administration of filgrastim on the same day as myelosuppressive cytotoxic chemotherapy have not been established. Because of the sensitivity of rapidly dividing myeloid cells to myelosuppressive cytotoxic chemotherapy, it is not recommended to administer filgrastim in the interval of 24 hours before and after the administration of these drugs. Preliminary data on a small number of patients who received filgrastim and 5-fluorouracil simultaneously indicate that the severity of neutropenia may increase. Possible interaction with other hematopoietic growth factors and cytokines has not been investigated in clinical trials.

Overdose

In cancer patients receiving filgrastim on myelosuppressive therapy, it is recommended to avoid the risk of excessive leukocytosis; filgrastim should be discontinued if the absolute neutrophil count exceeds 10000/mm3. In clinical trials of filgrastim in cancer patients receiving myelosuppressive chemotherapy, less than 5% of patients had leukocytosis with leukocyte counts >100000/mm3. No adverse events directly related to such leukocytosis have been described. Within 1-2 days after drug withdrawal, the number of circulating neutrophils usually decreases by 50%, with a return to normal after 1-7 days.

Dosage and administration method

By injection (preferred) or intravenously (infusion), once daily. The choice of route of administration depends on the specific clinical situation. Doses are set individually depending on indications, severity of process, patient's sensitivity. Treatment begins not earlier than 24 hours after chemotherapy. Cytotoxically induced neutropenia - usually 0.5 million units/kg per day; myeloablative therapy with bone marrow transplantation - 1 million units/kg per day; mobilization of hematopoietic progenitor cells - 1 million units/kg per day for 6 days; severe chronic and congenital neutropenia - initial dose of 1.2 million units/kg per day; malignant or recurrent neutropenia - initial dose of 0.5 million units/kg per day. Treatment is continued until normal neutrophil counts are restored (usually up to 14 days). After induction and consolidation therapy of acute myeloleukemia the duration of therapy may be increased up to 38 days.

Precautions

Therapy with filgrastim should only be carried out under the supervision of an oncologist or hematologist experienced in the use of such drugs.

Growth of malignant cells. G-CSF can induce growth of myeloid cells in vitro. Similar effects can be observed in vitro for some non-myeloid cells. Safety and efficacy of filgrastim in patients with myelodysplastic syndrome and chronic

myeloleukemia have not been established, so it is not indicated for these diseases. Particular attention should be paid to the differential diagnosis between blastotransformation of chronic myeloleukemia and acute myeloleukemia.

Leukocytosis. Given the possible risk associated with severe leukocytosis, the leukocyte count should be monitored regularly during treatment with filgrastim: if it exceeds 50000 cells/mm3, the drug should be withdrawn. When filgrastim is used to mobilize peripheral blood stem cells, it should be discontinued if the leukocyte count exceeds 100000/mm3.

Risks associated with high-dose chemotherapy. Particular caution should be exercised when treating patients receiving high-dose chemotherapy, as it has not been shown to improve the outcome of malignancy, while higher doses of chemotherapy have more severe toxicities, including cardiac, pulmonary, neurologic, and dermatologic reactions. Filgrastim monotherapy does not prevent thrombocytopenia and anemia associated with myelosuppressive chemotherapy. Because of the possibility of higher doses of chemotherapy (e.g., full doses according to regimens), the patient may be at greater risk of thrombocytopenia and anemia. Regular monitoring of platelet count and hematocrit is recommended. Particular caution should be exercised when using single-component or combination chemotherapy regimens known to cause severe thrombocytopenia.

Transformation into leukemia or preleukemia. Particular caution should be exercised when diagnosing severe chronic neutropenia to differentiate it from other hematologic diseases such as aplastic anemia, myelodysplasia, and myeloleukosis. Before treatment, a complete blood count and platelet count and bone marrow morphology and karyotype should be performed. If cytogenetic abnormalities appear in a patient with Kostmann syndrome, the risks and benefits of continued therapy must be carefully evaluated. If myelodysplastic syndrome or leukemia develops, the drug should be withdrawn. It is still unclear whether long-term treatment with filgrastim predisposes patients with severe congenital neutropenia (Kostmann syndrome) to the development of cytogenetic abnormalities, myelodysplasia and leukemia. Patients with hereditary neutropenia should have regular (every 12 months) morphological and cytogenetic studies of bone marrow.

Blood Formula. During the treatment period, especially during the first few weeks, the platelet count should be carefully monitored. If thrombocytopenia occurs (platelet count is stable <100000 cells/mm3), a dose reduction or temporary drug withdrawal should be considered. Other blood count changes requiring careful monitoring have also been observed, including anemia and a transient increase in myeloid progenitor cell counts.

Causes of transient neutropenia such as viral infections should be excluded before prescribing.

Spleen size (abdominal palpation) should be regularly monitored during treatment with filgrastim. Reducing the dose of filgrastim in the studies slowed or stopped the increase in the spleen.

Manufacturer

«Dong-Pha» South Korea

Storage conditions

Store in a dark place at 2-8℃ (do not freeze).

Keep out of the reach of children.

Shelf life

2 years.

Do not use after expiration date stated on the package.